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(54) Title: ORAL COMPOSITIONS COMPRISING POLYPHENOL HERBAL EXTRACTS

(57) Abstract: Disclosed are oral compositions comprising: an effective amount of a polyphenol herbal extract selected from the group consisting of magnolol, honokiol, tetrahydromagnolol, tetrahydrohonokiol, and mixtures thereof; an effective amount of a buffering agent; from about 40 % to about 99 % of one or more aqueous carriers; wherein the oral composition has a total water content of from about 5 % to about 70 %.

## ORAL COMPOSITIONS COMPRISING POLYPHENOL HERBAL EXTRACTS

### FIELD OF THE INVENTION

The present invention relates to oral compositions comprising polyphenol herbal extracts. More specifically, the present invention relates to oral compositions comprising magnolol, honokiol, and mixtures thereof for providing anti-microbial and bactericidal efficacy, as well as other oral health benefits.

### BACKGROUND OF THE INVENTION

Good oral hygiene may be at least in part achieved by brushing the teeth with an oral composition such as a dentifrice composition. A dentifrice composition is widely acknowledged as important in contributing to improving oral health, especially via a reduction in the incidence of dental caries and the build-up of tartar and dental calculus. Such conditions result from oral plaque, which may also lead to gingivitis and to periodontal disease. Periodontal disease remains a major cause of tooth loss in adults today. In addition, other oral health afflictions, such as staining of the tooth enamel and oral malodor (bad breath) may be reduced by regular tooth brushing with a dentifrice composition.

Dentifrices and other oral care products such as mouthwashes may contain anti-microbial agents, e.g., triclosan, stannous fluoride, chlorhexidine, quaternary ammonium salts, and camphorated parachlorophenol. However, although such products may provide some anti-microbial effect immediately after use, they may not deliver long lasting benefits or may only provide a limited anti-microbial effect. In some cases they may cause undesirable side effects such as staining, altered taste sensation, etc.

Certain crude drugs including Magnoliae cortex (from which the extracts magnolol and honokiol can be obtained) and Coptis rhizoma have previously been observed to inhibit the growth of cariogenic oral bacteria such as the *S. mutans* strain. For example, Japanese Laid-open Patent Application Nos. 57-85319 and 1-151512 to Tsurui Yakuhin Kogyo KK, published on May 28, 1982 and June 14, 1989, respectively, disclose that Magnoliae cortex and the above-mentioned extracts thereof have bactericidal action against *S. mutans* and are therefore useful as dental caries preventives. These references indicate that the disclosed caries preventatives may be applied directly into the oral cavity as they are, or may be mixed in other oral agents such as toothpaste, or in other suitable formulations such as troches or sublingual tables. However, these references do not provide any guidance as to how to formulate such preventatives into consumer-acceptable compositions.

Dentifrices comprising anti-microbial agents such as triclosan, herbal extracts such as goldenthread and honeysuckle, and metal ions are commercially available today. However, it is believed that such commercially available herbal dentifrices provide only a limited anti-microbial effect. In addition, aesthetic issues, such as unappealing appearance (e.g., brown or yellow color), that may make such dentifrice products unacceptable to some consumers exist in the currently available products. Consumers may also observe color changes in these types of products, which may cause them to question the product's quality. Finally, such dentifrices are also known to have stability issues in terms of loss of the anti-microbial agent, soluble fluoride, or both, from the compositions during storage and shelf life.

It has been now found that magnolol and honokiol are useful for breath freshening and for gum disease prevention as well as for caries prevention. Microbiological results indicate that both of these chemicals can be useful to prevent the growth of oral bacteria in the oral cavity. For example, it has been found that low levels of either of these chemicals (about 20 ppm of Honokiol and 50 ppm of Magnolol) can kill not only *Streptococcus mutans* (*S. mutans*), but also *Porphyromonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleum* (*F. nucleum*).

Therefore, although a number of dentifrice compositions have been described and many types of dentifrices and other oral care compositions are now commercially available, including those incorporating certain types of herbal

5        There remains a need for safe, efficacious, and stable oral compositions containing magnolol and/or honokiol in which the anti-microbial and bactericidal efficacy of these chemicals is present and which are aesthetically desirable to consumers. None of the existing art provides all of the advantages and benefits of the present invention.

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All publications, patent applications, and issued patents mentioned herein are hereby incorporated in their entirety by reference. Citation of any reference

is not an admission regarding any determination as to its availability as prior art to the claimed invention.

Herein, "comprising" means that other steps and other components which do not affect the end result can be added. This term encompasses the terms  
5 "consisting of" and "consisting essentially of."

Herein, "effective amount" means an amount of a compound or composition sufficient to significantly induce a positive benefit, preferably an oral health benefit, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the sound judgment of a skilled artisan.

10 All ingredients such as actives and other ingredients useful herein may be categorized or described by their cosmetic and/or therapeutic benefit or their postulated mode of action. However, it is to be understood that the actives and other ingredients useful herein can, in some instance, provide more than one cosmetic and/or therapeutic benefit or operate via more than one mode of action.  
15 Therefore, classifications herein are made for the sake of convenience and are not intended to limit an ingredient to the particular stated application or applications listed.

The oral composition of the present invention may be in the form of a toothpaste or dentifrice. The term "dentifrice", as used herein, means paste, gel,  
20 or liquid formulations unless otherwise specified. The dentifrice composition may be in any desired form, such as deep striped, surface striped, multi-layered, having the gel surrounding the paste, or any combination thereof. Alternatively, the oral composition may be one of the dentifrice compositions in a dual phase system comprising two dentifrice compositions contained in a physically  
25 separated compartment of a dispenser and dispensed side-by-side.

The term "dispenser", as used herein, means any pump, tube, or container suitable for dispensing toothpaste.

The term "oral composition" as used herein means the total composition that is delivered to the oral surfaces. The oral composition is a product, which in  
30 the ordinary course of usage, is not intentionally swallowed for purposes of systemic administration of particular therapeutic agents, but is rather retained in the oral cavity for a time sufficient to contact substantially all of the dental surfaces and/or oral tissues for purposes of oral activity. The oral compositions of the present invention are of course intended for human use, but they can with  
35 equal advantage be used for animals, such as household pets.



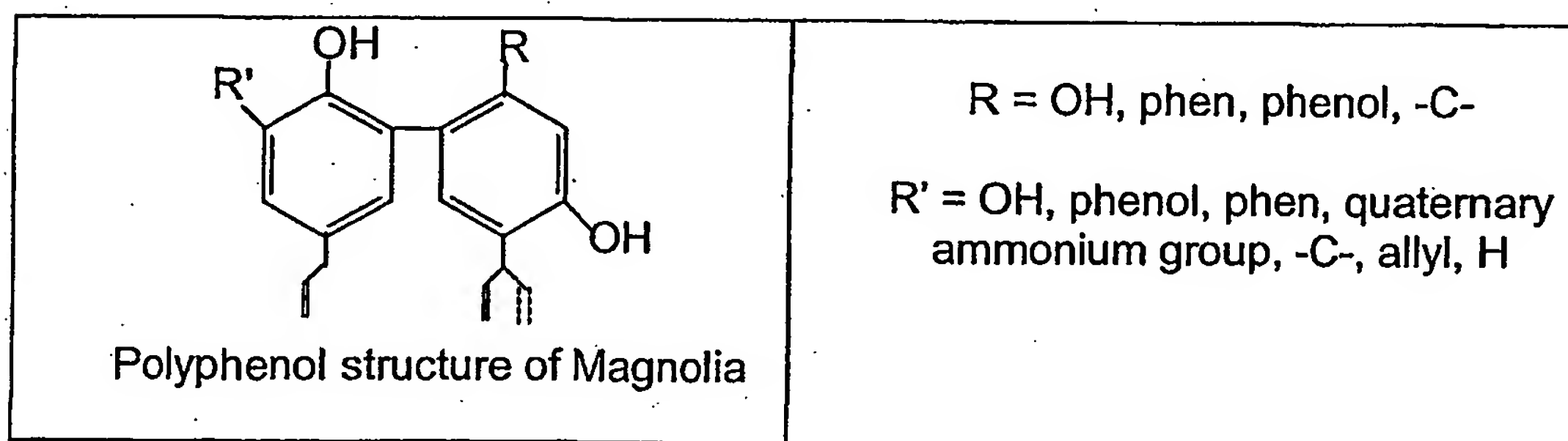
The term "aqueous carrier" as used herein means any safe and effective materials for use in the compositions of the present invention. Such materials include abrasive polishing materials, peroxide sources, alkali metal bicarbonate sources, anti-tartar agents, thickening materials, humectants, water, surfactants, titanium dioxide, antioxidants, metal ions, coloring agents, flavor systems, xylitol, sweetening agents, additional herbal agents, anti-microbial agents, and mixtures thereof.

The present compositions comprise essential components, as well as optional components. The essential and optional components of the compositions of the present invention are described in the following paragraphs.

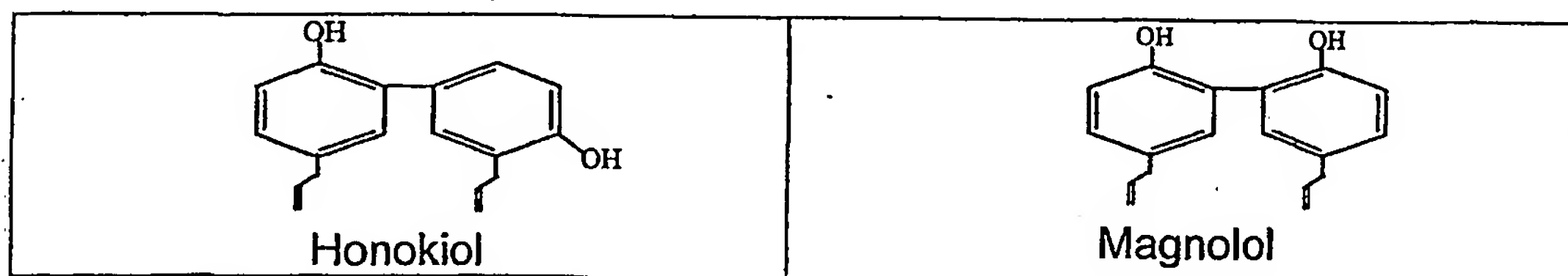
#### Polyphenol Herbal Extract

The compositions of the present invention include an effective amount of a polyphenol herbal extract, preferably selected from the group consisting of magnolol, honokiol, tetrahydromagnolol, tetrahydrohonokiol, and mixtures thereof, with magnolol, honokiol, and mixtures thereof being more preferred, and with honokiol being even more preferred. These chemicals can be extracted from *SiChuan Magnolia Officinalis*, a natural Chinese herb. Using supercritical fluid extraction techniques known to those of skill in the art, it is believed that the purity of such extracted chemicals higher than 95% can be obtained.

The polyphenol structure of magnolia is:



The chemical structures of magnolol and honokiol are:



The polyphenol herbal extracts herein are safe for humans. As noted above, they are natural crude drug extracts with no adverse reactions or side effects believed to be associated with their use. It is therefore believed that there is no true upper limit to the effective amount of the polyphenol herbal extracts that can be incorporated into the compositions of the present invention. However, it is believed that levels of from about 0.1% to about 2% as an active ingredient are sufficient to deliver their bactericidal effects.

The polyphenol herbal extracts can deliver oral health benefits due to their ability to inhibit the growth of certain bacteria, e.g., *S. mutans*, *P. gingivitis*, and *F. nuclearum*, when present in low concentrations, as well as their ability to kill such bacteria when present in relatively higher concentrations. These three bacteria are generally acknowledged to be among the main sources of oral diseases such as caries, gingivitis, and periodontal disease. They also contribute to breath malodor.

Minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) tests are conducted according to the following methods, benchmarking the polyphenol herbal extracts herein against triclosan, which is currently used as an anti-microbial agent in some commercially available oral care products.

The following table illustrates minimum inhibitory levels of polyphenol herbal extracts herein and triclosan for oral bacteria:

Table 1: MIC Test

	MIC for <i>S. mutans</i>	MIC for <i>P. gingivalis</i>	MIC for <i>F. nuclearum</i>
Honokiol	22 ppm	22 ppm	11 ppm
Magnolol	50 ppm	50 ppm	50 ppm
Triclosan	52 ppm	26 ppm	3 ppm

The culture time for the MIC Test is the entire time for culturing bacteria with magnolol and honokiol to demonstrate the inhibitory effect. As shown in Table 1, honokiol shows the strongest overall anti-microbial effect.

Table 2: MBC Test for Honokiol

Honokiol Concentration	173 ppm	86 ppm	43 ppm	22 ppm
Bacteria* →	SM/PG/FN	SM/PG/FN	SM/PG/FN	SM/PG/FN

Culture Time ↓				
2 min.	+/+/+	-/-/+	-/-/-	-/-/-
5 min.	+/+/+	+/+/+	-/-/-	-/-/-
10 min.	+/+/+	+/+/+	-/-/-	-/-/-
15 min.	+/+/+	+/+/+	+/-/+	-/-/+
30 min.	+/+/+	+/+/+	+/+/+	+/+/+

\*: "SM" indicates *S. mutans*; "PG" indicates *P. gingivalis*; "FN" indicates *F. nuclearum*.

"+" indicates positive result, i.e., bacteria will be killed within the correlative culture time.

5        "-" indicates negative result, i.e., bacteria will not be killed within the correlative culture time.

The culture time for the MBC Test is the period in which bacteria were cultured by honokiol, but the time for continuously culturing bacteria in agar after centrifuging is not included. As shown in Table 2, not only will relatively higher levels of honokiol more quickly kill each type of the above bacteria, but also

10        relatively lower levels will also kill each type if given sufficient time, e.g., about 30 minutes.

#### Fluoride Ion Source

Fluoride ion sources are well known for use in oral compositions as anti-

15        caries agents and are preferably contained in the compositions of the present invention, although the anti-microbial protection and other oral health benefits of polyphenol herbal extracts herein can be provided by compositions that do not contain fluoride. Fluoride ions are contained in a number of oral care compositions for this purpose, particularly toothpastes. Patents disclosing such

20        toothpastes include U.S. Pat. No. 3,538,230, Nov. 3, 1970 to Pader et al; U.S. Pat. No. 3,689,637, Sept. 5, 1972 to Pader; U.S. Pat. No. 3,711,604, Jan 16, 1973 to Colodney et al; U.S. Pat. No. 3,911,104, Oct. 7, 1975 to Harrison; U.S. Pat. No. 3,935,306, Jan. 27, 1976 to Roberts et al; and U.S. Pat. No. 4,040,858, Aug. 9, 1977 to Wason.

25        Application of fluoride ions to dental enamel serves to protect teeth against decay. A wide variety of fluoride ion-yielding materials can be employed as sources of soluble fluoride in the instant compositions. Examples of suitable fluoride ion-yielding materials are found in Briner et al; U.S. Pat. No. 3,535,421;



issued Oct. 20, 1970 and Widder et al; U.S. Pat. No. 3,678,154; issued July 18, 1972. Preferred fluoride ion sources for use herein include sodium fluoride, potassium fluoride and ammonium fluoride. Sodium fluoride is particularly preferred. Preferably the instant compositions provide from about 50 ppm to 10,000 ppm, more preferably from about 100 to 3000 ppm, of fluoride ions in the compositions that contact dental surfaces when used with the compositions of the present invention. Generally, the fluoride will be present at a level of from about 0.15% to about 2.5% by weight of the composition.

#### Buffering Agent

The present composition contains a buffering agent. If the oral composition is a dual phase system, a buffering agent will be present in both dentifrice compositions. Buffering agents, as used herein, refer to agents that can be used to adjust the pH of the compositions to a range of about pH 4 to about pH 10, with pH of about 4 to about 8 being preferred, and pH of about 5.5 to about 8 being more preferred. These agents include alkali metal hydroxides, carbonates, sesquicarbonates, borates, silicates, phosphates, imidazole, and mixtures thereof. Specific buffering agents include monosodium phosphate, trisodium phosphate, sodium hydroxide, potassium hydroxide, alkali metal carbonate salts, sodium carbonate, imidazole, pyrophosphate salts, citric acid, and sodium citrate. Buffering agents are used at a level of from about 0.1% to about 30%, preferably from about 1% to about 10%, and more preferably from about 1.5% to about 7%, by weight of the present composition. Preferred buffering agents are monosodium phosphate, trisodium phosphate, orthophosphate monohydrate, pyrophosphate salts, citric acid, sodium citrate, and mixtures thereof.

#### Pyrophosphate Salt

As mentioned above, pyrophosphate salts may be buffering agents. The pyrophosphate salts useful in the present compositions include the dialkali metal pyrophosphate salts, tetra alkali metal pyrophosphate salts, and mixtures thereof. Sodium acid pyrophosphate, disodium dihydrogen pyrophosphate ( $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ ), tetrasodium pyrophosphate ( $\text{Na}_4\text{P}_2\text{O}_7$ ), and tetrapotassium pyrophosphate ( $\text{K}_4\text{P}_2\text{O}_7$ ) in their unhydrated as well as hydrated forms are the preferred species. In compositions of the present invention, the pyrophosphate salt may be present in one of three ways: predominately dissolved, predominately undissolved, or a mixture of dissolved and undissolved pyrophosphate.

Compositions comprising predominately dissolved pyrophosphate refer to compositions where at least one pyrophosphate ion source is in an amount sufficient to provide at least about 1.0% free pyrophosphate ions. The amount of free pyrophosphate ions may be from about 1% to about 15%, preferably from about 1.5% to about 10%, and most preferably from about 2% to about 6%, by weight of the composition. Free pyrophosphate ions may be present in a variety of protonated states depending on the pH of the composition.

Compositions comprising predominately undissolved pyrophosphate refer to compositions containing no more than about 20% of the total pyrophosphate salt dissolved in the composition, preferably less than about 10% of the total pyrophosphate dissolved in the composition. Tetrasodium pyrophosphate salt and tetrapotassium pyrophosphate salt are the preferred pyrophosphate salts in these compositions, with tetrasodium pyrophosphate salt being the more preferred. Tetrasodium pyrophosphate may be the anhydrous salt form or the decahydrate form, or any other species stable in solid form in the dentifrice compositions. The salt is in its solid particle form, which may be its crystalline and/or amorphous state, with the particle size of the salt preferably being small enough to be aesthetically acceptable and readily soluble during use. The amount of pyrophosphate salt useful in making these compositions is any tartar control effective amount, and is generally from about 1.5% to about 15%, preferably from about 2% to about 10%, and most preferably from about 2.5% to about 8%, by weight of the composition. Some or all of the tetrasodium pyrophosphate may be undissolved in the product and present as tetrasodium pyrophosphate particles. Pyrophosphate ions in different protonated states (e.g.,  $\text{HP}_2\text{O}_7^{3-}$ ) may also exist depending upon the pH of the composition and if part of the tetrasodium pyrophosphate is dissolved.

Compositions may also comprise a mixture of dissolved and undissolved pyrophosphate salts. Any of the above mentioned pyrophosphate salts may be used.

The pyrophosphate salts are described in more detail in Kirk & Othmer, *Encyclopedia of Chemical Technology*, Third Edition, Volume 17, Wiley-Interscience Publishers (1982).

Optional agents to be used in place of or in combination with the pyrophosphate salt include such materials known to be effective in reducing calcium phosphate mineral deposition related to calculus formation. Agents

included are synthetic anionic polymers [including polyacrylates and copolymers of maleic anhydride or acid and methyl vinyl ether (e.g., Gantrez), as described, for example, in U.S. Patent 4,627,977, to Gaffar et al., as well as, e.g., polyamino propoane sulfonic acid (AMPS)], zinc citrate trihydrate, diphosphonates (e.g., EHDP; AHP), polypeptides (such as polyaspartic and polyglutamic acids), and mixtures thereof.

#### Aqueous Carriers

In preparing the present compositions, it is desirable to add one or more aqueous carriers to the compositions. Such materials are well known in the art and are readily chosen by one skilled in the art based on the physical and aesthetic properties desired for the compositions being prepared. Aqueous carriers typically comprise from about 40% to about 99%, preferably from about 70% to about 98%, and more preferably from about 90% to about 95%, by weight of the oral composition.

#### Triclosan

Other anti-microbial agents can also be present in the oral care compositions or substances of the present invention. A preferable agent is 5-chloro-2-(2,4-dichlorophenoxy)-phenol, commonly referred to as triclosan, and described in The Merck Index, 11th ed. (1989), pp. 1529 (entry no. 9573), in U.S. Patent No. 3,506,720, and in European Patent Application No. 0,251,591 of Beecham Group, PLC, published January 7, 1988. It is believed that the combination of triclosan and the polyphenol herbal extracts herein provides better anti-microbial protection effect than the polyphenol herbal extracts alone. Triclosan is believed to provide better antimicrobial effect against the *F. nuclearum* bacteria, as compared to the polyphenol herbal extracts herein. On the other hand, as noted in Table 2, the herbal extracts herein provide better anti-microbial efficacy against *S. mutans* and *P. gingivalis*. Therefore, the combination of a polyphenol herbal extract herein, preferably honokiol, with triclosan, is believed to provide the most complete overall anti-microbial effect.

Triclosan is preferably present at a level of from about 0.01% to about 1.5%, by weight of the composition.

#### Abrasive Polishing Materials

An abrasive polishing material is generally included in the toothpaste compositions herein. The abrasive polishing material contemplated for use in the compositions of the present invention can be any material which does not

excessively abrade dentin. The abrasive polishing material preferably has a calcium content of less than 23%. Typical abrasive polishing materials include silicas including gels and precipitates; aluminas; phosphates including orthophosphates, polymetaphosphates, and pyrophosphates; and mixtures thereof. Specific examples include dicalcium orthophosphate dihydrate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate, insoluble sodium polymetaphosphate, hydrated alumina, beta calcium pyrophosphate, calcium carbonate, and resinous abrasive materials such as particulate condensation products of urea and formaldehyde, and others such as disclosed by Cooley et al in U.S. Patent 3,070,510, issued Dec. 25, 1962. Mixtures of abrasives may also be used.

Silica dental abrasives of various types are preferred because of their unique benefits of exceptional dental cleaning and polishing performance without unduly abrading tooth enamel or dentine. The silica abrasive polishing materials herein, as well as other abrasives, generally have an average particle size ranging between about 0.1 to about 30 microns, and preferably from about 5 to about 15 microns. The abrasive can be precipitated silica or silica gels such as the silica xerogels described in Pader et al., U.S. Patent 3,538,230, issued Mar. 2, 1970, and DiGiulio, U.S. Patent 3,862,307, issued Jan. 21, 1975. Preferred are the silica xerogels marketed under the trade name "Syloid" by the W.R. Grace & Company, Davison Chemical Division. Also preferred are the precipitated silica materials such as those marketed by the J. M. Huber Corporation under the trade name, "Zeodent", particularly the silica carrying the designation "Zeodent 119". The types of silica dental abrasives useful in the toothpastes of the present invention are described in more detail in Wason, U.S. Patent 4,340,583, issued July 29, 1982. The abrasive in the compositions described herein is generally present at a level of from about 6% to about 70% by weight of the composition. Preferably, toothpastes contain from about 10% to about 50% of abrasive, by weight of the oral composition.

#### Peroxide Source

The present invention may include a peroxide source for whitening effect. The peroxide source is selected from the group consisting of hydrogen peroxide, calcium peroxide, urea peroxide, and mixtures thereof. The preferred peroxide source is calcium peroxide. The following amounts represent the amount of peroxide raw material, although the peroxide source may contain ingredients



other than the peroxide raw material. The present composition may contain from about 0.01% to about 10%, preferably from about 0.1% to about 5%, more preferably from about 0.2% to about 3%, and most preferably from about 0.3% to about 0.8% of a peroxide source, by weight of the composition.

5 Alkali Metal Bicarbonate Salt

The present invention may also include an alkali metal bicarbonate salt. Alkali metal bicarbonate salts are soluble in water and unless stabilized, tend to release carbon dioxide in an aqueous system. Sodium bicarbonate, also known as baking soda, is the preferred alkali metal bicarbonate salt. The alkali metal  
10 bicarbonate salt also may function as a buffering agent. The present composition may contain from about 0.5% to about 50%, preferably from about 0.5% to about 30%, more preferably from about 2% to about 20%, and most preferably from about 5% to about 18% of an alkali metal bicarbonate salt, by weight of the oral composition.

15 Anti-tartar Agents

Anti-tartar agents known for use in dental care products include phosphates. Phosphates include pyrophosphates, polyphosphates, polyphosphonates and mixtures thereof. Pyrophosphates are among the best known for use in dental care products. Pyrophosphate and polyphosphate ions  
20 are delivered to the teeth derive from pyrophosphate polyphosphate salts. The pyrophosphate salts useful in the present compositions include the dialkali metal pyrophosphate salts, tetra-alkali metal pyrophosphate salts, and mixtures thereof. Sodium acid pyrophosphate, disodium dihydrogen pyrophosphate ( $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$ ), tetrasodium pyrophosphate ( $\text{Na}_4\text{P}_2\text{O}_7$ ), and tetrapotassium  
25 pyrophosphate ( $\text{K}_4\text{P}_2\text{O}_7$ ) in their unhydrated as well as hydrated forms are the preferred species. While any of the above mentioned pyrophosphate salts may be used, tetrasodium pyrophosphate salt is preferred. Sodium polyphosphate and triethanolamine polyphosphates, for example, are preferred.

The pyrophosphate salts are described in more detail in Kirk & Othmer,  
30 *Encyclopedia of Chemical Technology*, Third Edition, Volume 17, Wiley-Interscience Publishers (1982). Additional anticalculus agents include pyrophosphates or polyphosphates disclosed in U.S. Patent No. 4,590,066 issued to Parran & Sakkab on May 20, 1986; polyacrylates and other polycarboxylates such as those disclosed in U.S. Patent No. 3,429,963 issued to  
35 Shedlovsky on February 25, 1969 and U.S. Patent No. 4,304,766 issued to



Chang on December 8, 1981; and U.S. Patent No. 4,661,341 issued to Benedict & Sunberg on April 28, 1987; polyepoxysuccinates such as those disclosed in U.S. Patent No. 4,846,650 issued to Benedict, Bush & Sunberg on July 11, 1989; ethylenediaminetetraacetic acid as disclosed in British Patent No. 490,384 dated February 15, 1937; nitrilotriacetic acid and related compounds as disclosed in U.S. Patent No. 3,678,154 issued to Widder & Briner on July 18, 1972; polyphosphonates as disclosed in U.S. Patent No. 3,737,533 issued to Francis on June 5, 1973, U.S. Patent No. 3,988,443 issued to Ploger, Schmidt-Dunker & Gloxhuber on October 26, 1976 and U.S. Patent No. 4,877,603 issued to Degenhardt & Kozikowski on October 31, 1989. Anticalculus phosphates include potassium and sodium pyrophosphates; sodium tripolyphosphate; diphosphonates, such as ethane-1-hydroxy-1,1-diphosphonate, 1-azacycloheptane-1,1-diphosphonate, and linear alkyl diphosphonates; linear carboxylic acids; and sodium zinc citrate.

Agents that may be used in place of or in combination with the pyrophosphate salt include such known materials as synthetic anionic polymers including polyacrylates and copolymers of maleic anhydride or acid and methyl vinyl ether (e.g., Gantrez), as described, for example, in U.S. Patent 4,627,977, to Gaffar et al.; as well as, e.g., polyamino propoane sulfonic acid (AMPS), zinc citrate trihydrate, polyphosphates (e.g., tripolyphosphate; hexametaphosphate), diphosphonates (e.g., EHDP; AHP), polypeptides (such as polyaspartic and polyglutamic acids), and mixtures thereof.

#### Additional Aqueous Carriers

The present invention compositions in the form of toothpastes typically contain some thickening material or binders to provide a desirable consistency. Preferred thickening agents are carboxyvinyl polymers, carrageenan, hydroxyethyl cellulose, and water soluble salts of cellulose ethers such as sodium carboxymethylcellulose and sodium hydroxyethyl cellulose. Natural gums such as gum karaya, xanthan gum, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents can be used in an amount from about 0.1% to about 15%, by weight of the dentifrice composition.

Another optional component of the compositions desired herein is a humectant. The humectant serves to keep toothpaste compositions from

hardening upon exposure to air and certain humectants can also impart desirable sweetness of flavor to toothpaste compositions. Suitable humectants for use in the invention include glycerin, sorbitol, polyethylene glycol, propylene glycol, and other edible polyhydric alcohols. The humectant generally comprises from about 5 0% to 70%, and preferably from about 15% to 55%, by weight of the composition.

Water employed in the preparation of commercially suitable oral compositions should preferably be of low ion content and free of organic impurities. The compositions herein will contain a water level of from about 5% 10 to about 70%, preferably from about 7% to about 40%, and more preferably for toothpastes from about 10% to about 30%, by weight of the composition. The amounts of water include the free water which is added plus that which is introduced with other materials, such as with sorbitol, silica, surfactant solutions, and/or color solutions.

#### 15 Other Ingredients

The present compositions may also comprise surfactants, also commonly referred to as sudsing agents. Suitable surfactants are those which are reasonably stable and foam throughout a wide pH range. The surfactant may be anionic, nonionic, amphoteric, zwitterionic, cationic, or mixtures thereof. Anionic 20 surfactants useful herein include the water-soluble salts of alkyl sulfates having from 8 to 20 carbon atoms in the alkyl radical (e.g., sodium alkyl sulfate) and the water-soluble salts of sulfonated monoglycerides of fatty acids having from 8 to 20 carbon atoms. Sodium lauryl sulfate and sodium coconut monoglyceride sulfonates are examples of anionic surfactants of this type. Other suitable 25 anionic surfactants are sarcosinates, such as sodium lauroyl sarcosinate, taurates, sodium lauryl sulfoacetate, sodium lauroyl isethionate, sodium laureth carboxylate, and sodium dodecyl benzenesulfonate. Mixtures of anionic surfactants can also be employed. Many suitable anionic surfactants are disclosed by Agricola et al., U.S. Patent 3,959,458, issued May 25, 1976. 30 Nonionic surfactants which can be used in the compositions of the present invention can be broadly defined as compounds produced by the condensation of alkylene oxide groups (hydrophilic in nature) with an organic hydrophobic compound which may be aliphatic or alkyl-aromatic in nature. Examples of suitable nonionic surfactants include poloxamers (sold under trade name 35 Pluronic), polyoxyethylene, polyoxyethylene sorbitan esters (sold under trade

name Tweens), fatty alcohol ethoxylates, polyethylene oxide condensates of alkyl phenols, products derived from the condensation of ethylene oxide with the reaction product of propylene oxide and ethylene diamine, ethylene oxide condensates of aliphatic alcohols, long chain tertiary amine oxides, long chain tertiary phosphine oxides, long chain dialkyl sulfoxides, and mixtures of such materials. The amphoteric surfactants useful in the present invention can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be a straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water-solubilizing group, e.g., carboxylate, sulfonate, sulfate, phosphate, or phosphonate. Other suitable amphoteric surfactants are betaines, specifically cocamidopropyl betaine. Mixtures of amphoteric surfactants can also be employed. Many of these suitable nonionic and amphoteric surfactants are disclosed by Gieske et al., U.S. Patent 4,051,234, issued September 27, 1977. The present composition typically comprises one or more surfactants each at a level of from about 0.25% to about 12%, preferably from about 0.5% to about 8%, and most preferably from about 1% to about 6%, by weight of the composition.

Titanium dioxide may also be added to the present composition. Titanium dioxide is a white powder which adds opacity to the compositions. Titanium dioxide generally comprises from about 0.25% to about 5%, by weight of the composition. Similarly, mica may added to the present compositions in order to provide opacity and to further provide a shimmery or glittery appearance. Mica generally comprises from about 0.1 to about 5%, by weight of the composition.

Antioxidants are generally recognized as useful in compositions such as those of the present invention and may be included herein. Antioxidants are disclosed in texts such as Cadenas and Packer, The Handbook of Antioxidants, © 1996 by Marcel Dekker, Inc. Antioxidants that may be included in the oral care composition or substance of the present invention include, but are not limited to Vitamin E, ascorbic acid (vitamin C), Uric acid, carotenoids, Vitamin A, flavonoids, herbal antioxidants, melatonin, aminoindoles, lipoic acids and mixtures thereof. Vitamins E and C are preferred, with levels of from about 0.01% to about 0.10% being desirable, and about 0.01% to about 0.05% being preferred.

Other metal ions may further be added to enhance the breath protection efficacy of the polyphenol. Such ions include but are not limited to, zinc ions; stannous, and copper ions, such as  $Zn^{2+}$ ,  $Sn^{+}$ , and  $Cu^{+}$ . Because living cells and proteins have hydroxy, amino and carboxy groups on their surfaces, it is believed that such metal ions could tightly link polyphenol with *S. mutans* and other bacteria, to enhance the reduction in volatile sulfur compounds that contribute to oral malodor.

Coloring agents may also be added to the present composition. The coloring agent may be in the form of an aqueous solution, preferably 1% coloring agent in a solution of water. Color solutions generally comprise from about 0.01% to about 5%, by weight of the composition.

A flavor system can also be added to the compositions. Suitable flavoring components include tea mint, oil of wintergreen, oil of peppermint, oil of spearmint, clove bud oil, menthol, anethole, methyl salicylate, eucalyptol, cassia, 1-menthyl acetate, sage, eugenol, parsley oil, oxanone, alpha-irisone, marjoram, lemon, orange, propenyl guaethol, cinnamon, vanillin, ethyl vanillin, heliotropine, 4-cis-heptenal, diacetyl, methyl-para-tert-butyl phenyl acetate, and mixtures thereof. Coolants may also be part of the flavor system. Preferred coolants in the present compositions are the paramenthan carboxyamides such as N-ethyl-p-menthan-3-carboxamide (known commercially as "WS-3") and mixtures thereof. A flavor system is generally used in the compositions at levels of from about 0.001% to about 5%, by weight of the composition.

The present invention may also include xylitol. Xylitol is a sugar alcohol that is used as a sweetener and/or humectant. Xylitol may also provide a therapeutic effect, such as anti-caries effect or anti-bacterial effect. The present compositions typically comprise xylitol at a level of from about 0.01% to about 25%, preferably from about 3% to about 15%, more preferably from about 5% to about 12%, and most preferably from about 9% to about 11%. Alternatively, if xylitol is used only as a sweetener, it may be present at a lower level, such as from about 0.0005% to about 5%, by weight of the dentifrice composition.

Sweetening agents other than xylitol can be added to the compositions. These include saccharin, dextrose, sucrose, lactose, maltose, levulose, aspartame, sodium cyclamate, D-tryptophan, dihydrochalcones, acesulfame, and mixtures thereof. Various coloring agents may also be incorporated in the present invention. Sweetening agents and coloring agents are generally used in



toothpastes at levels of from about 0.005% to about 5%, by weight of the composition.

Additional herbal agents, including but not limited to, golden thread extract and honeysuckle extract, may also be present in the compositions herein at levels of from about 0.01% to about 0.05%. Such herbal agents are believed to provide anti-bacteria efficacy.

In addition to triclosan, other anti-microbial agents can also be present in the oral care compositions or substances of the present invention. Other specific antimicrobial agents include chlorhexidine, triclosan monophosphate, and essential oils including thymol, geraniol, carvacrol, citral, hinokitiol, eucalyptol, and mixtures thereof. Triclosan and other agents of this type are disclosed in Parran, Jr. et al., U.S. Patent 5,015,466, issued May 14, 1991, and U.S. Patent 4,894,220, Jan. 16, 1990 to Nabi et al. These agents may be present at levels of from about 0.01% to about 1.5%, by weight of the composition.

Also included among such other anti-microbial agents are water insoluble non-cationic antimicrobial agents such as halogenated diphenyl ethers, phenolic compounds including phenol and its homologs, mono and poly-alkyl and aromatic halophenols, resorcinol and its derivatives, bisphenolic compounds and halogenated salicylanilides, benzoic esters, and halogenated carbanilides. The water soluble antimicrobials include quaternary ammonium salts and bis-biquanide salts, among others. Triclosan monophosphate is also a suitable water soluble antimicrobial agent. The quaternary ammonium agents include those in which one or two of the substitutes on the quaternary nitrogen has a carbon chain length (typically alkyl group) from about 8 to about 20, typically from about 10 to about 18 carbon atoms while the remaining substitutes (typically alkyl or benzyl group) have a lower number of carbon atoms, such as from about 1 to about 7 carbon atoms, typically methyl or ethyl groups. Dodecyl trimethyl ammonium bromide, tetradecylpyridinium chloride, domiphen bromide, N-tetradecyl-4-ethyl pyridinium chloride, dodecyl dimethyl (2-phenoxyethyl) ammonium bromide, benzyl dimethylstearyl ammonium chloride, cetyl pyridinium chloride, quaternized 5-amino-1,3-bis(2-ethyl-hexyl)-5-methyl hexa hydropyrimidine, benzalkonium chloride, benzethonium chloride and methyl benzethonium chloride are exemplary of typical quaternary ammonium antibacterial agents. Other compounds are bis[4-(R-amino)-1-pyridinium] alkanes as disclosed in U.S. Patent 4,206,215, issued June 3, 1980, to Bailey.



Stannous salts such as stannous pyrophosphate and stannous gluconate and other antimicrobials such as copper bisglycinate, copper glysinate, zinc citrate, and zinc lactate may also be included. Also useful are enzymes, including endoglycosidase, papain, dextranase, mutanase, and mixtures thereof. Such agents are disclosed in U.S. Patent 2,946,725, Jul. 26, 1960, to Norris et al. and in U.S. Patent 4,051,234, September. 27, 1977 to Gieske et al.

Also suitable for use as anti-microbial agents herein are phthalic acid and its salts including, but not limited to those disclosed in U.S. Pat. 4,994,262, Feb. 19, 1991, preferably magnesium monopotassium phthalate, chlorhexidine (Merck Index, no. 2090), alexidine (Merck Index, no. 222; hexetidine (Merck Index, no. 4624); sanguinarine (Merck Index, no. 8320); benzalkonium chloride (Merck Index, no. 1066); salicylanilide (Merck Index, no. 8299); domiphen bromide (Merck Index, no. 3411); cetylpyridinium chloride (CPC) (Merck Index, no. 2024; tetradecylpyridinium chloride (TPC); N-tetradecyl-4-ethylpyridinium chloride (TDEPC); octenidine; delmopinol, octapinol, and other piperidino derivatives; nicin preparations; zinc/stannous ion agents; antibiotics such as augmentin, amoxicillin, tetracycline, doxycycline, minocycline, and metronidazole; and analogs and salts of the above; methyl salicylate; hydrogen peroxide; metal salts of chlorite and mixtures of all of the above.

#### Method of Treatment

The present invention additionally relates to a method for providing anti-microbial oral health benefits including plaque removal, caries prevention, gingivitis prevention, and breath freshness to a human or to an animal. The method of treatment herein comprises contacting a subject's dental enamel surfaces and mucosa in the mouth with the oral compositions according to the present invention. The method of treatment may be by brushing with a dentifrice or rinsing with a dentifrice slurry or mouthrinse. Other methods include contacting a topical oral gel, dentures product, mouthspray, or other form with the subject's teeth and oral mucosa. The subject may be any person or lower animal whose tooth surface contacts the oral compositions. For example, a method of treatment may include a person brushing the teeth or rinsing the mouth of a pet such as a dog or cat, or a domestic animal or any other animal kept in captivity, with one of the compositions herein.

Examples & Method of Manufacturing

The following examples further describe and demonstrate embodiments within the scope of the present invention. These examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope.

**EXAMPLES 1-3**

<b>Component</b>	<b>Ex. 1</b>	<b>Ex. 2</b>	<b>Ex. 3</b>
Magnolol	1.0	1.0	-
Honokiol	-	-	1.0
Sodium Fluoride, USP	0.243	0.312	0.243
Sorbitol Solution, USP	36.757	36.0	37.037
Precipitated Silica Abrasive (Zeodent 119)	20.0	20.0	20.0
Treated Water	16.0	16.0	16.0
Triclosan, USP	0.28	-	0.28
Carbomer 956	0.250	-	0.250
Saccharin, Sodium, USP	0.15	0.25	0.15
Xanthan Gum	1.1	1.1	1.1
Glycerin, USP	2.0	11.0	2.0
Sodium Alkyl Sulfate Solution (27.9%)	7.5	7.5	7.5
Polyethylene Glycol-300	4.0	5.0	4.0
Flavor	0.8	1.0	0.8
Coloring agent FD&C Blue Dye #1	-	0.002	-
Titanium Dioxide, Rutile, USP	0.5	-	0.5
Trisodium Phosphate, Dodecahydrate	0.9	0.2	0.9
Monosodium Phosphate	0.4	-	0.4
Orthophosphate Monohydrate	-	1.35	-
Carboxymethylcellulose, Sodium, 9M31XF	-	1.0	-
<b>TOTAL</b>	<b>100.0</b>	<b>100.0</b>	<b>100.0</b>

**EXAMPLES 4-6**

<b>Component</b>	<b>Ex. 4</b>	<b>Ex.5</b>	<b>Ex. 6</b>
Magnolol	-	0.5	0.5
Honokiol	1.0	0.5	0.5
Sodium Fluoride, USP	0.312	0.243	0.312
Sorbitol Solution, USP	36.0	36.537	37.037
Precipitated Silica Abrasive (Zeodent 119)	20.0	20.0	20.0
Treated Water	16.0	16.0	16.0
Triclosan, USP	-	0.28	-
Carbomer 956	-	0.250	-
Saccharin, Sodium, USP	0.25	0.15	0.25
Xanthan Gum	1.1	1.1	1.1
Glycerin, USP	11.0	2.0	11.0
Sodium Alkyl Sulfate Solution (27.9%)	7.5	7.5	7.5
Polyethylene Glycol-300	5.0	4.0	5.0
Flavor	1.0	0.8	1.0
Coloring agent FD&C Blue Dye #1	0.002	-	0.002
Titanium Dioxide, Rutile, USP	-	0.5	-
Trisodium Phosphate, Dodecahydrate	0.2	0.9	0.2
Monosodium Phosphate	-	0.4	-
Orthophosphate Monohydrate	1.35	-	1.35
Carboxymethylcellulose, Sodium, 9M31XF	1.0	-	1.0
<b>TOTAL</b>	<b>100.0</b>	<b>100.0</b>	<b>100.0</b>

**EXAMPLE 7: Breath Protection Efficacy Test**

5 In order to illustrate additional benefits of the preferred embodiments of the present invention, in the following Example, breath protection efficacy of five compositions over four hours is compared by conducting a Halimeter test according to the following procedure.

All test participants test breath level with the Halimeter in the morning before brushing the teeth, drinking, or eating (the 0 hour measurement). After the morning measurement, all participants eat the same food and drink the same beverage for breakfast, e.g., a cup of milk and a piece of bread. After breakfast, all eating and drinking is prohibited, although one cup of water drunk all at one time may be allowed, preferably after the second measurement and about 30 minutes prior to the third measurement. After eating, each participant brushes his or her teeth and tongue for one minute using the assigned test composition in equal weight amounts. After brushing, 15 ml of water is used to rinse the mouth. One hour later, the second Halimeter measurement is taken; two hours later the third measurement is taken; three hours later the fourth measurement is taken; four hours later the fifth measurement is taken. Just prior to each Halimeter measurement, participants are requested not to speak and to hold the lips closed for 30 seconds.

The Halimeter detects the presence of volatile sulfur compounds in the breath. The volatile sulfur compounds include hydrogen sulfide, methyl mercaptan, dimethylsulfide, ethylsulfide and dimethyldisulfide, all of which contribute to bad breath. Thus, the higher the Halimeter reading, the less breath protection that is provided.

Each data point (value of Halimeter reading) below represents an average for all test participants using the same test composition at the same time. Data collected from participants that did not correctly follow the test procedure is excluded.

Example 7, Table 3: Four Hours Breath Protection Efficacy Test (N= 11 for each test composition)

Test Composition	Halimeter Reading (ppb) vs. Time				
	0 hour	1 hour	2 hours	3 hours	4 hours
Honokiol Dentifrice with Triclosan	365	29	70	98	126
Magnolol Dentifrice with Triclosan	320	37	74	101	130
LMZ <sup>1</sup>	307	57	109	230	267
CREST MANY-IN-ONE <sup>2</sup>	354	50	94	137	192

CREST KC**	378	63	107	170	239
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1 LMZ ("Liang Mian Zhen") is a Chinese herbal dentifrice product that is commercially available from LMZ Limit Corp., Liuzhou, China. It contains the herbal extract of *liangmian Zhen*.

2 CREST MANY-IN-ONE ("MIO") and CREST KC are commercially  
 5 available dentifrice products from the Procter & Gamble Company, Cincinnati Ohio, USA, and Procter & Gamble (China), Ltd. Neither product contains polyphenol herbal extracts. MIO contains goldenthread extract, honeysuckle extract, and triclosan. KC does not contain other herbal extracts or triclosan.

The foregoing example illustrates that a composition comprising a  
 10 polyphenol herbal extract herein provides better breath protection efficacy over an extended time period (e.g., at least one hour and preferably longer, e.g., at least four hours) as compared to currently marketed formulations that do not contain such extracts. Although all of the test compositions provide some breath protection just after initial use, the Halimeter readings for the non-polyphenol  
 15 containing compositions increase over time as compared to all polyphenol-containing compositions, indicating that that breath malodor worsens over time.

#### EXAMPLE 8: Stability Performance Test

In the following example, a dentifrice paste formulation and a dentifrice gel  
 20 formulation according to the present invention, see Table 4 below, are measured for stability over 4½ months at storage conditions of 40°C and 60% relative humidity. These conditions believed to commonly exist during storage, especially in Asian countries. Stability data for these compositions is given in Tables 5 and 6.

25 In Table 7, percentage of the named actives lost in a commercially available herbal dentifrice product after 4½ months at storage conditions of 40°C and 60% relative humidity is given.

Analytical measurements are made by methods known to those of skill in the art.

30 Example 8, Table 4

Component	Paste	Gel
Magnolol	1 or 0	1 or 0 or 0.5
Honokiol	0 or 1	0 or 1 or 0.5
Sodium Fluoride, USP	0.243	0.243



Sorbitol Solution, USP	37.037	36.0
Precipitated Silica Abrasive	19.120	20.0
Treated Water	25.0	15.255
Carbomer 956	0.250	-
Saccharin, Sodium, USP	0.15	0.25
Xanthan Gum	1.1	0.2
Glycerin, USP	2.0	11.0
Sodium Alkyl Sulfate Solution (27.9%)	7.5	7.5
Polyethylene Glycol-300	4.0	5.0
Flavor	0.8	1.0
Coloring agent FD&C Blue Dye #1	-	0.002
Titanium Dioxide, Rutile, USP	0.5	-
Trisodium Phosphate, Dodecahydrate	0.9	0.9
Monosodium Phosphate	0.4	-
Orthophosphate Monohydrate	-	0.65
Carboxymethylcellulose, Sodium, 9M31XF	-	1.0
TOTAL	100.0	100.0

Example 8, Table 5: Paste Stability Measurement

Component	Initial	1 <sup>st</sup> month	3 <sup>rd</sup> month	4.5 <sup>th</sup> month	% Loss
Honokiol	0.95%	0.89%	0.83%	0.80%	15%
Soluble Fluoride	282 ppm	275 ppm	265 ppm	262 ppm	7%
pH	7.06	7.00	6.95	6.78	4%

Example 8, Table 6: Gel Stability Measurement

Component	Initial	1 <sup>st</sup> month	3 <sup>rd</sup> month	4.5 <sup>th</sup> month	% Loss
Honokiol	0.96%	0.90%	0.87%	0.86%	10%
Soluble Fluoride	286 ppm	278 ppm	269 ppm	261 ppm	9%
pH	6.76	6.50	6.42	6.38	5%

Example 8, Table 7: Current Commercial Product Stability Measurement

Product/Component	% Loss over 4.5 months
CREST MIO/Herbal Extracts <sup>1</sup>	37%

1 See Example 7, above, MIO/goldenthread and honeysuckle extracts.

From the foregoing data, it can be seen that the percent loss of the polyphenol herbal extract herein is significantly less than that of the commercial product. In addition, the soluble fluoride content of the compositions herein  
5 remains at an acceptably high level.

In addition to the above stability measurements, overall aesthetic appearance of the tested products after 4½ months at storage conditions of 40°C and 60% relative humidity is observed. The color of the Table 7 current commercial product is observed to have changed from light yellow or white/green  
10 to deep brown or gray/deep green at the head of the dentifrice tube. It is believed that such color changes also occur in other commercially available herbal dentifrices. It is herein believed that such an appearance does not impart a perception of freshness or cleaning efficacy to some consumers. In addition, color changes may cause consumers to doubt the product's quality or to feel that  
15 the product has experienced spoilage.

In contrast, the light blue color of the paste and gel products of the present invention, see Table 4, is observed to be unchanged after the 4½ months of storage. It is believed that the aesthetic appearance of the compositions of the present invention is more pleasing to many consumers than  
20 the appearance of current products. Furthermore, since the present compositions are shown to exhibit stability, it is believed that any desired dentifrice color to meet any consumer needs can be obtained herein and maintained over storage, shelf life and usage times.

#### 25 Method of Preparation

The dentifrice compositions are prepared as follows. Add the water, polyphenol herbal extract, and saccharin to a mixing vessel. Dissolve the polyphenol herbal extract and the saccharin in the water. Disperse the thickening agents in the glycerin. Add this mixture of dispersed thickening  
30 agents in glycerin to the mixing vessel, mix well, and heat to at least 40° C. Mix the flavor in the surfactant and add to the mixture. Add the polyethylene glycol, propylene glycol, and sodium carbonate (if used). Mix well. Next, add the titanium dioxide and the silica. After mixing, add the sodium bicarbonate (if used) and sodium alkyl sulfate. Finally, add the polyphosphate and calcium peroxide (if

used). Continue stirring the mixture until homogeneous. Triclosan (if used) is added to the glycerin or propylene glycol, as it is hydrophobic and cannot be mixed together with water.

5 It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to one skilled in the art without departing from the scope of the present invention.

## WHAT IS CLAIMED IS:

1. An oral composition comprising:
  - a. an effective amount of a polyphenol herbal extract selected from the group consisting of magnolol, honokiol, tetrahydromagnolol, tetrahydrohonokiol, and mixtures thereof;
  - b. an effective amount of a buffering agent;
  - c. from about 40% to about 99% of one or more aqueous carriers;wherein the oral composition has a total water content of from about 5% to about 70%.
2. The composition of Claim 1 further comprising from about 0.15% to about 2.5% of a fluoride ion source.
3. The oral composition according to Claim 1 comprising from about 0.1% to about 2% of the polyphenol herbal extract.
4. The oral composition of Claim 1 wherein the aqueous carriers are materials selected from the group consisting of abrasive polishing materials, peroxide sources, alkali metal bicarbonate sources, anti-tartar agents, thickening materials, humectants, water, surfactants, titanium dioxide, antioxidants, metal ions, coloring agents, flavor systems, xylitol, sweetening agents, additional herbal agents, anti-microbial agents, and mixtures thereof.
5. The oral composition according to Claim 4 wherein the anti-microbial agent is triclosan.
6. The oral composition according to Claim 1 or Claim 5 wherein the herbal polyphenol extract is honokiol.
7. The oral composition according to Claim 6 wherein the abrasive polishing material is selected from the group consisting of silicas, aluminas, phosphates, orthophosphates, polymetaphosphates, and mixtures thereof.

8. The oral composition according to Claim 1 wherein the composition has less than about 35% loss of the polyphenol herbal extract after about 4 ½ months storage at 40°C and 60% relative humidity.
9. The oral composition of Claim 1 or Claim 7 wherein the composition is a dentifrice having a total water content of from about 10% to about 30%.
10. A method for providing anti-microbial oral health benefits to a human or to an animal comprising contacting the oral cavity surfaces with the oral composition according to Claim 1.



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 00/11258

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/05 A61K7/26 A61K35/78 A61P31/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 35599 A (DAEWOONG PHARMACEUTICAL CO., LTD) 2 October 1997 (1997-10-02) the whole document	1,3,4,7
A	--- CHEMICAL ABSTRACTS, vol. 133, no. 12, 18 September 2000 (2000-09-18) Columbus, Ohio, US; abstract no. 168207m, JUNG, JONG-PYUNG: "Antibacterial compositions comprising magnolol and honokiol from Machili cortex" XP002901552 page 897, column 2 & KR 9 607 923 A (DAE WOONG PHARMACEUTICAL CO., LTD) 17 June 1996 (1996-06-17) abstract --- -/--	1-9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 December 2000

Date of mailing of the international search report

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# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 00/11258

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 08 175945 A (KAO CORP) 9 July 1996 (1996-07-09) abstract ---	1-9
A	JP 08 175946 A (KAO CORP) 9 July 1996 (1996-07-09) abstract -----	1-9

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 00/11258

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 10 is directed to a therapeutic method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition (see PCT-Article 17, Rule 39.1. iv).
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 00/11258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9735599 A	02-10-1997	KR 176015 B AU 2180097 A	20-03-1999 17-10-1997
KR 9607923 A	17-06-1996	NONE	
JP 08175945 A	09-07-1996	NONE	
JP 08175946 A	09-07-1996	NONE	